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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/011,940	03/03/1999	MICHAEL A. NAUCK	864861USWO	1535

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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/011,940	NAUCK ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 January 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *41-44,48,51 and 56*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1, 17-19, 21, 23-25, 32-35, 45-46, 49-50 and 52-54*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s)._____

10. ☒ Other: *See attached "Advisory Action".*

3/5/04

Bennett Celsa
Primary Examiner
Art Unit: 1639

ADVISORY ACTION

Applicant's After-Final Amendment dated 1/12/04 is hereby acknowledged.

Status of the Claims

Claims 1, 17-19, 21, 23-25, 32-35, 41-46 and 48-55 are currently pending and under consideration.

Claims 41-44, 48, 51 and 55 are allowed.

Claims 1, 17-19, 21, 23-25, 32-35, 45-46, 49-50 and 52-54 are rejected.

OutstandingObjection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 102/103

1. Claims 1, 17-19, 21, 23-25, 32, 35, 45 and 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Baer et al. Diabetes Vol. 34 (Nov. 1985) pages 1108-112.

Baer et al. teach providing "non-alimentary nutrition" to a rat (e.g. "a patient in need of parenteral nutrition") by "parenterally" infusing (e.g. intravenously i.e. 1.6ug/kg in aqueus solution) a nutrient solution (e.g. comprising glucose and amino acids) and gastric inhibitory peptide (e.g. GIP which is an insulinotropic peptide). See entire article, especially abstract and page 1109, left column. The reference further teaches that mean plasma concentrations that provide plateau levels of GIP. E.g. see Figures; pages 1109-1110.

Discussion

Applicant's arguments directed to the above anticipation rejection were considered but deemed nonpersuasive for the following reasons.

Applicant's argument that the Baer reference is directed to a "study" and not a "treatment" is not persuasive since the Baer method reference teaches applicant's claimed method steps regardless of the reason why such steps were performed. Applicant's argument regarding "treatment" is irrelevant since the present claims are not so limited and further the reference performs the same exact steps using a composition within the presently claimed scope. The reference amount of nutrients is within the presently claimed scope of "nutritively effective amount"; such amounts not being defined in the specification and amount being to some extent, nutritive. Applicant's teaching away argument is not persuasive since the above is an anticipation rejection and not an obviousness rejection. Additionally, the reference host (e.g.a rat), receiving both nutrients and an insulinotropic peptide, is within the scope of "a patient in need of parenteral nutrition" as presently claimed. Again applicant's argument's regarding the benefits of their method verse the perceived drawbacks (e.g. "deleterious rise in the plasma blood glucose level") of the reference method is not relevant in regards to anticipation wherein the reference method meets applicant's presently claimed method steps.

Accordingly, the above anticipation rejection is hereby maintained.

2. Claims 1, 17-19, 21, 23-25, 32, 35, 45 and 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Amland et al. Scandinavian Journal of Gastroenterology, Vol. 20, No. 3 April 1985 pages 321-324.

Amland et al. teach (e.g. see page 321col. 2-page 322) providing "non-alimentary nutrition" to "fasting" humans (e.g. "a patient in need of parenteral nutrition") by "parenterally" infusing (e.g. intravenously i.e. in aqueus solution) a nutrient solution (e.g. comprising glucose) and gastric inhibitory peptide (e.g. GIP which is an insulinotropic peptide). The reference further teaches that mean plasma concentrations that provide plateau levels of GIP. E.g. see page 322 under "Plasma GIP".

Discussion

Applicant's arguments directed to the above anticipation rejection were considered but deemed nonpersuasive for the following reasons.

Applicant's argument that the Amland reference is directed to "experimental research" and not a "treatment" is not persuasive since the Amland reference method teaches applicant's claimed method steps regardless of the reason why such steps were performed. Applicant's argument regarding "treatment" is irrelevant since the present claims are not so limited and further the reference performs the same exact steps using a composition within the presently claimed scope. Applicant's argument's regarding the unperceived (e.g. by the reference) benefits of their method is not relevant in regards to anticipation wherein the reference method meets applicant's presently claimed method steps.

Accordingly, the above anticipation rejection is hereby maintained.

3. Claims 1, 17, 19, 21, 23-25, 32-35, 45 and 52-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Habener, U.S. Pat. No 5,614,492 (3/97: filed 9/91 or earlier).

Habener "492 disclose the use of GLP 1 and its derivatives (e.g. col. 7) to treat both diabetes and hyperglycemia (e.g. see col. 6, lines 1-10) due to the peptide's "insulinotropic" activity (e.g. see col. 5, line 60-70). "Parenteral administration" of GLP 1 and its derivatives in pharmaceutical compositions comprising carbohydrates (e.g. lactose), polyamino acids: controlled release formulations comprising lipid derivatives (e.g. liposomes) e.g. see bottom of col. 9 to top of col. 10) as well as conjugates thereof (e.g. see col. 10, lines 13-26) anticipate the presently claimed invention. Further Example 11 (e.g. col. 21-28, especially "meal studies") disclose the administration of GLP-1 both during a meal (e..g 50% CHO; 30% fat; 20% protein: see e.g. col. 22, lines 55-67) and postprandial to both NORMAL and non-diabetic patients with the successful control of plasma glucose levels. See also patent claims 1 and 9 (and dependent claims thereon) teaching the use of GLP-1 and derivatives to treat diabetes and hyperglycemia.

Accordingly, the parenteral administration of GLP-1 and its derivatives before/during/after meals that both contained and generated CHO (e.g. especially glucose) anticipates the presently claimed invention. See also patent claims which additionally disclose the treatment of both diabetes and hyperglycemia utilizing GLP-1 containing compositions. The reference clearly incorporates the addition of compounds that are within the scope of the term "nutrients" (e.g. lactose, amino acids) both as

separate compounds or as conjugates (e.g. see col. 9-10). Additionally, the patent reference further teaches administration of GLP compounds with a meal which presumably would contain nutrients (e.g. see col. 9-10 and examples).

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed partially persuasive.

Applicant argues that Example 11 is directed to the parenteral administration of GLP-1 but the non-parenteral (e.g. oral) administration of nutrients (e.g. by standard breakfast meal) . This argument was found persuasive and the above rejection modified (e.g. to remove claims 18 and, 46) addressing this aspect of the above rejection.

Applicant argues that the Habener reference lack of discussing nutrition precludes the reference from meeting the present claim limitations directed to a "nutritively effective amount".

This argument is not persuasive. For purposes of prosecution, the law dicatates that the claims are to be interpreted as broadly as reasonable without incorporating specification limitations into the presently claimed invention. The specification fails to specifically define concentration amounts/ranges that constitute a "nutritively effective amounts"; accordingly, the reference incorporation of nutrients within the scopes of applicant's claims would provide some degree of nutrition when administered parenterally as taught by the reference. Accordingly, applicant's claim limitation directed to "nutrively effective amounts" is met.

Thus, the above rejection, as modified in response to applicant's argument, is hereby maintained.

4. Claims 1, 17-19, 21, 23-25, 32-35, 45, 46, 49-50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Specification disclosure as to the state of the prior art in view of Habener, U.S. Pat. No. 5,614,492 (3/97: filed 9/91 or earlier) and/or Eng US Pat. No. 5,424,286 (6/95) .

The specification on pages 1-2 and page 10, lines 15 describes the state of the prior art regarding the necessity for providing parenteral nutrition to patients having "disturbed glucose metabolism" (e.g. surgery patients, shock etc) as well as to malnourished patients while overcoming the hyperglycemia that accompanies parenteral nutrition. Coadministration of insulin with parenteral nutrition in order to overcome the hyperglycemia problem has its drawbacks (e.g. see page 1, lines 13-25).

The State of the Prior Art as described in the specification differs from the presently claimed invention which incorporates the use of "insulinotropic peptides" (e.g. GLP-1 and its derivatives) in parenteral nutrition compositions which comprise nutrients (e.g. glucose or glucose generating compounds) for alimentary nutrition or to treat hyperglycemic states.

However, both the Habener and Eng Patent references teach the "insulinotropic" nature of GLP-1 and related peptides e.g. the ability of these peptides to endogenously generate insulin and thus combat hyperglycemia.

Additionally, the prior/sequential and co-administration of these "insulinotropic" peptides with a meal containing nutrients (e.g. which include glucose or generate glucose) and the peptides concomitant ability to obtain normalized glucose levels is both disclosed and suggested by the Habener and/or Eng patents (e.g. see Habener, Example 11, col. 21-28 and patent claims addressing treatment of diabetes and hyperglycemia; e.g. see Eng at col. 1, lines 49-67 disclosing lowering of meal-related glucose levels by parenteral administration of GLP-1 and GLIP which effect was also found with other "insulinotropic" peptides (e.g. exendins) alone or in combination (including sequential) with GLP-1 (e.g. see Eng col. 2, lines 35-40; col. 5, lines 14-20; Example 2 (col. 6-7); Example 5 relating to diabetics; and patent claims 5-6.

The determination of optimal amounts of "insulinotropic" peptides and/or nutrients taken sequentially or in combination is well within the skill of the art as well as the determination of optimal delivery formulations (e.g. tablets, pills, delayed release etc.) and time of delivery (e.g. coadministered, sequential etc.).

One of ordinary skill in the art would be motivated to substitute the "insulinotropic" peptides disclosed by the Eng or Habener references for insulin in "parenteral" formulations as disclosed in the Specification, due to the problematic use of insulin as discussed in the specification and in view of the ability of "insulinotropic peptides" to endogenously produce insulin as taught by the Eng and/or Habener references.

Accordingly, the incorporation of "insulinotropic" peptides (e.g. GLP-1 or its derivatives) into parenteral formulations containing "nutrients" to treat diabetics, non-

diabetics (e.g. hyperglycemia) or malnourished individuals would have been obvious to one of ordinary skill in the art at the time of applicant's invention in view of the Habener and/or Eng references which demonstrate that administration of these peptides to obtain normalized glucose levels; regardless of the cause of hyperglycemia (meal/diabetes/hyperglycemia etc.).

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that neither Habener nor Eng teaches providing a treatment for delivering pareneteral nutrition including nutritively effective amount of nutrients and at least one insulinotropic peptide. This argument was considered but deemed nonpersuasive for the following reasons.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the Examiner's motivation for substituting the Eng/Habener "insulinotropic peptides" for insulin in parental feeding compositions comprising insulin and nutrient(s) disclosed in the Specification represents "impermissible hindsight based upon Applicant's own disclosure as a basis for rejecting claims".

Initially, it is noted that it is legally permissible for the PTO to utilize specification admissions as to the state of the prior art, especially as described in the "Background of

the Invention" as in the above-cited rejection; and use thereof does not constitute impermissible hindsight on the part of the Examiner.

Additionally, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the present instance it was known to parenterally administer insulin and nutrients to patients in need thereof (e.g. surgery, shock etc.); with insulin combatting the hyperglycemia resulting from the nutrients. However, "serious drawbacks" to insulin administration was "short half life" , "significant variation in blood sugar levels" and "hypoglycemia".

BOTH the Eng and Habener teach the functional equivalency of insulin and insulinotropic peptides in combatting hyperglycemia in diabetics and non-diabetics. Additional motivation to substitute an insulinotropic peptide for insulin is further provided by the references' teaching of the beneficial addressing of insulin's "serious drawbacks" (as outlined above) through the use of insulinotropic peptides. For example Habener in columns 5-6 teach GLP analogs "insulinotropic activity" and the use of such analogs to treat "non-diabetics" e.g. hyperglycemic patients. Further, Eng at col. 1,

lines 49-67 teaches that parenterally administered exendin peptides (e.g. GLIP): "**significantly lowered the meal-related increases in blood glucose concentration, and** the plasma concentrations of insulin and glucagon. In patients with NIDDM, the treatment reduced the requirement for insulin by **8 fold**. In patients with IDDM, the GLIP treatment **lowered the insulin required by one half.** This glucose-dependent activity is a very desirable characteristic for a therapeutic agent that can be used to treat DM **avoiding tile complications of hypoglycemic side effects**" (bolded for emphasis).

Accordingly, the secondary references provide strong motivation, separately or in combination, to substitute "insulinotropic" peptides for insulin in the conventionally known parenteral formulations comprising nutrients and insulin *without the use of impermissible hindsight.*

Applicant further argues that "It was the inventors who first recognized that more nutrients can be delivered parenterally with the administration of an insulinotropic peptide".

This argument was considered but deemed nonpersuasive for the following reasons. Applicant's arguments are not commensurate in scope regarding the rejected claims which do not provide claim limitations which correspond to applicant's arguments. The above combination of references render the presently claimed invention prima facie obvious. Applicant has not provided any evidence of unexpected results *commensurate* with the presently claimed invention.

Accordingly, the above rejection is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
March 5, 2004